

NEW STILBENES WITH VASCULAR DAMAGING ACTIVITY

- Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.
- Compounds able to damage neovasculture have advantages in the treatment of disease. For example, attacking tumour vasculature has several important advantages over a direct attack on the tumour. In particular the endothelial cells of tumour vasculature are more genetically stable than those of the tumour itself and are therefore less likely to become resistant to the damaging agent. Thus a major problem in conventional anti-tumour chemotherapy, that of drug resistance, is circumvented by this approach. Furthermore, since the endothelial cells of the tumour vasculature, unlike the tumour cells themselves, are similar between different solid tumour types, vascular damaging agents are able to attack a wide range of tumour types.
- A number of tubulin-binding agents including the stilbenes combretastatin A1, combretastatin A4 (D. J. Chaplin *et al.*, British J. Cancer 27, S86-S88 (1996)) and combretastatin A4 phosphate (D.J. Chaplin *et al.*, Anticancer Research 19, 189-196, (1999)) are known to selectively damage neovasculture of solid tumours in animal models. While there are reports of the activity of other analogues of combretastatin A4 in tubulin binding assays, in cytotoxicity assays and in tumour models there have been no reports of the vascular damaging activities of analogues. Since the activity of

tubulin-binding compounds against *in vitro* assays are poor predictors of selective vascular damaging activity and activity of such compounds *in vivo* can also be mediated by direct antimitotic effects on the tumour itself, no prediction can be made of the selective vascular damaging activity of known or novel analogues of the combretastatins from published reports. Thus compounds which have the advantages
5 of a selective anti-vascular mechanism given above, rather than acting through a direct effect on the tumour tissue itself, are not apparent.

We have found a series of novel *cis*-stilbenes with vascular damaging activity. These
10 compounds specifically damage newly-formed vascular endothelium, especially that associated with solid tumours, without affecting the normal, established vascular endothelium of the host species. Such compounds are of use in the prophylaxis and treatment of cancers involving solid tumours and in other diseases where there is inappropriate formation of new vasculature such as diabetic retinopathy, psoriasis,
15 rheumatoid arthritis, macular degeneration and the formation of atherosclerotic plaques.

Known vascular-damaging stilbenes, combretastatin A1, combretastatin A4 and combretastatin A4 phosphate have a 4-methoxy group in the "B" ring. The
20 compounds of the invention lack a 4-methoxy group in the ring corresponding to the "B" ring of combretastatin A4. Several studies suggest that substituting alternative groups for the 4-methoxy group in the B-ring of combretastatin A4 would considerably reduce biological activity:

25 In *J. Med. Chem* 1991, 34, 2579-2588, Cushman *et al.* state, regarding analogues of combretastatin A4: "the presence of a 4-methoxy group in the B-ring plays a very important role for this compound to be highly cytotoxic". Replacement of the 4-methoxy group with chlorine, for example, gave compounds that were three to four orders of magnitude less potent against a panel of five different cell lines.

In J. Med. Chem. 1998, 41, 3022-3032 Ohsumi *et al.* disclose anilino analogues of combretastatin A4 in which the replacement of the B-ring 4-methoxy group by either a methyl group or a chlorine atom gave a reduction in biological potency of 8.5-fold and 13.5-fold respectively.

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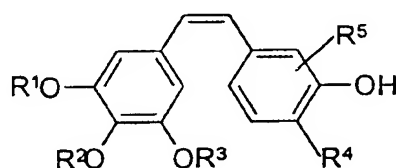
Similarly in Brit. J. Cancer 1995, 71, 705-711 Woods *et al.* disclose analogues of combretastatin with reduced potency. For example the 4-methyl compound shows 3.5 to 36-fold reduction in potency against four cell lines compared to the 4-methoxy compound.

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It cannot be anticipated from the above studies that compounds in which the B-ring 4-methoxy group is replaced would retain anti-vascular activity. It is particularly unexpected that replacing the B-ring methoxy group of combretastatin A4 would result in a compound with similar potency as a vascular damaging agent.

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Thus according to one aspect of the invention we provide a compound of formula (1):



(I)

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Wherein:

R¹, R² and R³ are each independently alkyl,

25 R⁴ is alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl or halo,

R⁵ is hydrogen, alkoxy, alkyl, alkylthio, hydroxy or halo,

and the pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

As used herein the term "alkyl", alone or in combinations, means a straight or branched-chain alkyl group containing from one to seven, preferably a maximum of four, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy.

The term "halogen" means fluorine, chlorine, bromine or iodine.

An alkenyl group may be for example an olefinic group containing from two to seven carbon atoms for example methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene and t-butylene. An alkynyl group may be for example an ethynyl, propynyl or butynyl group.

Where one or more functional groups in compounds of formula (1) are sufficiently basic or acidic the formation of salts is possible. Suitable salts include pharmaceutically acceptable salts for example acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates, salts derived from inorganic bases including alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and salts derived from organic amines such as morpholine, piperidine or dimethylamine salts.

Prodrugs of the invention are compounds which upon administration to a mammal produce compounds of formula (1). Such prodrugs can be for example converted within the mammal by hydrolysis. Prodrugs are preferably ester derivatives of the phenolic hydroxy group contained in compounds of formula (1) such as, for example, phosphate esters, carboxylate esters, sulphate esters and carbonates.

Preferred compounds of the invention are those of formula 1 in which R^1 , R^2 and R^3 are all methyl, and prodrugs thereof

Further preferred compounds of the invention are those of formula 1 in which R^1 , R^2 and R^3 are all methyl and R^5 is hydrogen and prodrugs thereof

- 5 Still further preferred compounds of the invention are those of formula 1 in which R^1 , R^2 and R^3 are all methyl, R^5 is hydrogen and R^4 is alkyl or halo and prodrugs thereof

Preferred prodrugs of the invention are phosphate esters. Particularly preferred prodrugs of the invention are dihydrogen phosphate esters.

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Specifically preferred compounds of the invention are:

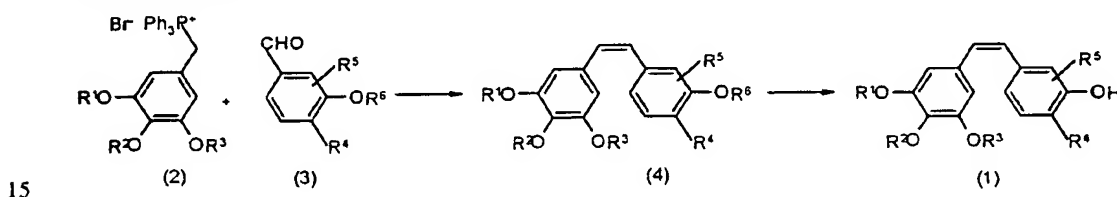
(Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

- 15 (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate

Compounds of the invention can be prepared by any process known to a person skilled in the art. Compounds of formulae (1) can be prepared by a number of processes as generally described hereinbelow and more specifically in the Examples hereinafter. In
20 the general preparations described below it may be necessary to employ protecting groups which are then removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art. In the following process description, the symbols R^1 , R^2 , R^3 , R^4 and R^5 , when used in the formulae depicted are to be
25 understood to represent those groups described above in relation to formula (1) unless otherwise indicated

In one general example compounds of formula (1) can be prepared by Wittig olefin synthesis involving reaction of a phosphonium salt of formula (2) with a strong base,
30 for example an alkyllithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether

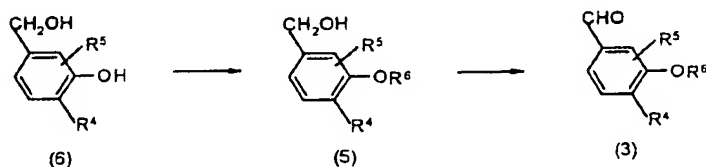
or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a temperature of between about -100°C to about 30°C followed by treatment with an aldehyde of formula (3) in which R⁶ is a protecting group, to give an intermediate of formula (4). The synthesis of compounds of formula (1) is then completed by removal of the group R⁶. Suitable protecting groups R⁶ include trialkylsilyl, for example t-butyl-
 5 butyldimethylsilyl, and allyl. Where R⁶ is a trialkylsilyl group it may be removed, for example, by treatment with a quaternary ammonium fluoride such as tetrabutylammonium fluoride in an ether solvent such as tetrahydrofuran at a temperature of about -30°C to about 40°C conveniently at or near ambient
 10 temperature. Where R⁶ is an allyl group it may be removed for example by treatment with a palladium(0) complex such as tetrakis(triphenylphosphine)Pd(0) in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of about -40°C to about 40°C conveniently at or near ambient temperature, in the presence of an allyl scavenger such as morpholine.



Aldehydes of formula (3) can be prepared by any process known to a person skilled in the art. In one general example an aldehyde of formula (3) can be prepared from an alcohol of formula (5) by oxidation with a suitable oxidising agent. Suitable oxidising
 20 agents include the Dess-Martin reagent and manganese dioxide. Alcohols of formula (5) can be prepared by application of standard methods of organic synthesis including the selective protection of phenols of formula (6). Where the protecting group R⁶ is a trialkylsilyl group, for example t-butyl-
 25 butyldimethylsilyl, alcohols of formula (5) may be prepared, for example, by treatment of a phenol of formula (6) with a strong base, for example an alkylolithium such as n-butyllithium or t-butyllithium or a metal hydride such as sodium hydride in a solvent such as an ether solvent for example diethyl ether or tetrahydrofuran or in a solvent such as a hydrocarbon solvent for example toluene at a

temperature of between about -100°C to about 40°C followed by treatment with *tert*-butylchlorodimethylsilane.

- Phenols of formula (6) are either known or may be prepared from known compounds using standard methods of organic synthesis.



- Compounds of formula (1) may also be prepared from other compounds of formula (1) by chemical modification. Examples of such chemical modifications that may be applied are standard alkylation, halogenation, oxidation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents.

- Prodrugs of compounds of formula (1) can be prepared by any process known to a person skilled in the art. Processes for the preparation of prodrugs of compounds of formula 1 include standard acylation, sulphation and phosphorylation reactions. In one general example dihydrogen phosphate esters of compounds of formula (1) can be prepared by treatment of the corresponding di-*t*-butylphosphate esters with an acid, for example hydrochloric acid or trifluoroacetic acid, in a solvent such as a chlorinated solvent, for example dichloromethane, at a temperature of from about -20°C to about 40°C , conveniently at room temperature.

- Compounds according to the invention are able to destroy tumour vasculature and vasculature that has been newly formed while leaving unaffected normal, mature vasculature. The ability of the compounds to act in this way may be determined by the tests described hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

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The compounds of the invention may be administered as a sole therapy or in combination with other treatments. Thus the invention includes compositions for the treatment of neovascularisation which compositions contain an effective amount of a cis-stilbene or prodrugs thereof as hereinbefore defined. The invention also includes

10 the use in the preparation of a composition for the treatment of neovascularisation of a cis-stilbene or prodrugs thereof as hereinbefore defined. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, vincristine, vinorelbine,

15 paclitaxel and docetaxel; platinum derivatives for example cisplatin and carboplatin; alkylating agents, for example melphalan, chlorambucil, busulphan, ifosfamide and cyclophosphamide; antimetabolites, for example methotrexate, 5-fluorouracil, cytosine arabinoside, gemcitabine and hydroxyurea; antitumour antibiotics for example bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C,

20 dactinomycin and mithramycin; enzymes, for example asparaginase; topoisomerase inhibitors for example etoposide, teniposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab and trastuzumab; anti-hormones for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene, anastrozole,

25 letrozole, vorazole, exemestane, flutamide, nilutamide and bicalutamide; anti-growth factor compounds for example EGFr tyrosine kinase inhibitors VEGFr kinase inhibitors and PDGFr tyrosine kinase inhibitors; and anti-angiogenesis agents such as angiostatin, endostatin and thalidomide. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

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For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, 5 rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal 10 administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a 15 particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.1 to 10mg/kg.

20

BIOLOGICAL ACTIVITY

The following test was used to demonstrate the activity of compounds according to the invention.

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Activity against tumour vasculature measured by fluorescent dye.

The following experiment further demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using 30 the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). At least three animals were used in control and treated

groups. The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μ m sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels. Examples of the activity of compounds of the invention in this test are given in the table:

Compound of Example	Dose (mg/kg)	% Reduction in Functional Vascular Volume
1	50	88
3	50	27
5	50	20

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

(Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

A solution of 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (491mg) in anhydrous tetrahydrofuran (10ml) at room temperature was treated slowly with a 1.1M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1ml). After 30 minutes crushed ice (5ml) and diethylether (30ml)

were added and the aqueous phase extracted with diethylether (5 portions of 5ml).

The combined extracts were washed with water (3 portions of 10ml) and brine (10ml), dried (MgSO₄) and concentrated under reduced pressure to give a solid.

Recrystallisation from ethyl acetate/hexane gave the title compound (208mg) as a

5 white solid m.p. 123-125°C. nmr: δ H (500MHz, d₆-DMSO) 2.07 (s, 3H), 3.57 (s, 6H), 3.62 (s, 3H), 6.40 (d, J = 12Hz, 1H), 6.46 (d, J = 12 Hz, 1H), 6.56 (s, 2H), 6.61 (dd, J = 8Hz, 2Hz, 1H), 6.76 (d, J = 1.7Hz, 1H), 6.98 (d, J = 8Hz, 1H), 9.21 (s 1H).

The 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene
10 used as starting material in the above preparation was prepared as follows:

A suspension of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (848mg) in dry tetrahydrofuran (50ml) at -78°C was treated dropwise with n-butyllithium (0.9ml of a 1.8M solution in hexane) and the mixture allowed to warm to -40°C and stir for 1h.

The mixture was recooled to -78°C and a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (390mg) in tetrahydrofuran (40ml) added slowly. After a further
15 2h the mixture was allowed to warm to room temperature before being poured into ice water (20ml). The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (3 portions of 20ml) and brine (2 portions of 20ml), dried (MgSO₄) and concentrated under reduced pressure to give an
20 oil. Purification by chromatography on silica gel, eluting with petroleum ether / ethyl acetate (90:10) gave 1-(3-*tert*-butyldimethylsilyloxy-4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (456mg) as a red oil.

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde used as starting material in the
25 above preparation was prepared as follows:

A solution of Dess-Martin periodinane (187mg) in dichloromethane (4ml) was treated slowly with a solution of 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (100mg) in dichloromethane (4ml) and the mixture stirred for 1h at room temperature.

Diethylether (10ml) was added followed by aqueous sodium thiosulphate solution
30 (10ml) and the mixture stirred for 15 minutes. The aqueous phase was extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with aqueous

sodium thiosulphate solution (3 portions of 10ml), water (3 portions of 10ml) and brine (2 portions of 10ml), dried (MgSO₄) and concentrated under reduced pressure to give a yellow solid. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzaldehyde (85mg).

The 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol used as starting material in the above preparation was prepared as follows:

A solution of 3-hydroxy-4-methylbenzyl alcohol (275mg) in dry tetrahydrofuran (15ml) at -78°C was treated slowly with *n*-butyllithium (1.2ml of a 1.8M solution in hexane) and the mixture stirred for 15 minutes before being allowed to warm to room temperature and stir for a further 30 minutes. A solution of *tert*-butylchlorodimethylsilane (287mg) in tetrahydrofuran (10ml) was added and the mixture stirred for 16h. Water (20ml) was added and the mixture extracted with diethylether (5 portions of 20ml) and the combined extracts were washed with water (2 portions of 10ml) and brine (20ml), dried (MgSO₄) and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with petroleum ether / diethyl ether (50:50) gave 3-*tert*-butyldimethylsilyloxy-4-methylbenzyl alcohol (390mg).

EXAMPLE 2

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate

Trifluoroacetic acid (0.22mL, 2.95mmol) was added dropwise to a stirred solution of (Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate (401mg, 0.82mmol) and dichloromethane (16mL). The mixture was stirred at room temperature overnight. Solvent was removed *in vacuo*, and the residue azeotroped four times with toluene. The colourless oil was triturated with ether to give the title compound as a white solid (181mg, 58%) m.p. 109-113°C. nmr: δ H (500MHz, d₆-DMSO) 2.39 (s, 3H), 3.81 (s, 6H), 3.87 (s, 3H), 6.69 (d, J=12Hz, 1H), 6.74 (d,

J=12Hz, 1H), 6.78 (s, 2H), 7.07 (d, J=8Hz, 1H), 7.28 (d, J=8Hz, 1H), 7.49 (s, 1H), 9.0 (bs, 2H).

(Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate was
5 prepared as follows:
Di-*tert*-butylphosphoramidite (498mg, 2.00mmol) in dichloromethane (1mL) was
added to a solution of (Z)-1-(3-hydroxy-4-methylphenyl)-2-(3,4,5-
trimethoxyphenyl)ethene (300mg, 1.00mmol), 1*H*-tetrazole (182mg, 2.60mmol) in
dichloromethane (3mL) under nitrogen. After 2h, magnesium monoperoxyphthalate
10 hexahydrate (1.24g, 2.00mmol) was added in portions. After stirring for a further 2h,
the reaction mixture was partitioned between ethyl acetate and water; the aqueous
phase was extracted (ethyl acetate x2); the combined organic extracts were washed
(water x2, brine x1); dried (MgSO₄) and concentrated *in vacuo*. Flash
chromatography, eluting with 33% ethyl acetate/hexane, gave (Z)-2-methyl-5-[2-
15 (3,4,5-trimethoxyphenyl)ethenyl]phenyl di-*tert*butyl phosphate as a yellow oil (401mg,
82%).

EXAMPLE 3

20 (Z)-1-(4-fluoro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

This compound was isolated directly from the Wittig reaction between 3,4,5-
trimethoxybenzyltriphenylphosphonium bromide and 3-*tert*-butyldimethylsilyloxy-4-
fluorobenzaldehyde (340mg) performed in an analogous manner to that of Example 1.
25 There was obtained the title compound (80mg) as a colourless oil. nmr: (300MHz, d6-
DMSO) 3.59 (s, 6H), 3.63 (s, 3H), 6.46 (d, J=12Hz, 1H), 6.48 (d, J=12Hz, 1H), 6.54
(s, 2H), 6.68 (m, 1H), 6.90 (dd, J=8.8, 2.1Hz, 1H), 7.06 (dd, J=11.4, 8.4Hz, 1H), 9.80
(s, 1H).

30 The following compounds were prepared in an analogous manner to that of Example
1:

EXAMPLE 4(Z)-1-(4-chloro-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

- 5 From (Z)-1-(3-*tert*-butyldimethylsilyloxy-4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)ethene (240mg) there was obtained the title compound (121mg) as a colourless oil. nmr: (300MHz, d6-DMSO) 3.59 (s, 6H), 3.63 (s, 3H), 6.49 (m, 2H), 6.54 (s, 2H), 6.71 (dd, J=8.2, 0.9Hz, 1H), 6.93 (d, J=0.9Hz, 1H), 7.25 (d, J=8.2Hz, 1H), 10.11 (bs, 1H).m/e 320 (M+).

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EXAMPLE 5(Z)-1-(4-ethyl-3-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene

- From (Z)-1-(3-*tert*-butyldimethylsilyloxy-4-ethylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (926mg) there was obtained the title compound (208mg) as a white solid m.p. 105-107°C, nmr: δ H (300MHz, CDCl₃) 1.02 (t, J=7.6Hz, 3H), 2.6 (q, J=7.5Hz, 2H) 3.7 (s, 6H), 3.8 (s, 3H), 4.6 (bs, 1H), 6.4 (d, J = 12Hz, 1H), 6.5 (d, J = 12 Hz, 1H), 6.5 (s, 2H), 6.7 (s, 1H), 6.8 (d, J = 7.6Hz, 1H), 7.0 (d, J = 7.6Hz, 1H).

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